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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

| EXAMINER | |
|---|---|
| KUBELIK, ANNE R | |
| **ART UNIT** | **PAPER NUMBER** |
| 1638 | |

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/840,743 | FISCHER ET AL. | |
| | Examiner | Art Unit | |
| | Anne R. Kubelik | 1638 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *34-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *34-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 19 March 2004 has been entered.

2. Claims 34-46 are pending.

3. The abstract is not descriptive of the instant invention. A new abstract is required that is clearly indicative of the invention to which the claims are directed. The objection is repeated for the reasons of record as set forth in the Office action mailed 22 September 2003. Applicant's arguments filed 19 March 2004 have been fully considered but they are not persuasive.

Applicant urges that the abstract is accurate (response pg 5).

This is not found persuasive because the instantly claimed invention is not drawn to DMT polypeptides or to DMT nucleic acids, but to methods of modulating development in a plant, including organ identity, organ number, meristem size, flowering time, etc.

4. The title of the invention is not descriptive of the instant invention. A new title is required that is clearly indicative of the invention to which the claims are directed. Note that titles can be up to 500 characters long. The objection is repeated for the reasons of record as set forth in the Office action mailed 22 September 2003. Applicant's arguments filed 19 March 2004 have been fully considered but they are not persuasive.

Applicant urges that they are not clear as to what changes should be made (response pg 5).

This is not found persuasive because the instantly claimed invention is not drawn to DMT nucleic acids, but to methods of modulating development in a plant, including organ identity, organ number, meristem size, flowering time, etc.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Claim Objections*

6. Claims 40-45 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. If Applicant assertions about DMT are correct, a DMT polynucleotide would inherently modulate organ identity, organ number, meristem size, methylation and expression of the MEDEA gene and would inherently delay flowering time; thus, the claims fail to further limit parent claims 34.

### *Claim Rejections - 35 USC § 112*

7. Claims 34-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of using an expression cassettes encoding SEQ ID NO:2 to produce late-flowering plants, does not reasonably provide enablement for methods of using a multitude of expression cassettes encoding DMT proteins with 80% identity to SEQ ID NO:2 to modify development in a plant. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection is modified from the full enablement rejection set forth in the Office action mailed 22 September 2003, as applied to claims 1-2, 6-8, 13, 15-21, 24-26 and 30-33, due to amendment of the claims. Applicant's arguments filed 19 March 2004 have been fully considered but they are not persuasive.

The claims are broadly drawn to methods of using a multitude of expression cassettes encoding DMT proteins with 80% identity to SEQ ID NO:2 to modify development in a plant.

The instant specification, however, only provides guidance for characterization of *Arabidopsis dmt-1 and -2* mutants, which have fertilization-independent endosperm development, created by T-DNA mutagenesis and use of the T-DNA to isolate the genomic clone, SEQ ID NO:1, which encodes SEQ ID NO:2 (example 1); isolation of *dmt-3*, made by another T-DNA insertion, and the conclusion that all mutant alleles are loss-of-function alleles (example 2); RNA analysis in *dmt/dmt* mutants to show that they have no *MEDEA* RNA expression (example 3), generation of transgenic plants in which DMT is overexpressed from the CaMV 35S promoter to create plants in which *MEDEA* RNA levels are increased (example 3); these plants are late-flowering (example 5); a BLAST search of SEQ ID NO:2 to show that DMT is a member of the HhH-GPD superfamily of DNA repair enzymes and has three domains that correspond to conserved regions of in other HhH-GPD family members (example 4); a BLAST search of databases to identify numerous related proteins and identification of consensus sequences for DMT, SEQ ID NOs:71-73 (example 4); speculation that DMT is a 5-methylcytosine glycosylase

and that mutants have hypomethylation of the genome (example 5); and expression analysis of the DMT promoter, using a DMT promoter-GUS fusion gene (example 6).

The instant specification fails to provide guidance for nucleic acids encoding DMT proteins with 80% identity to SEQ ID NO:2 and methods of using a multitude of expression cassettes encoding proteins with 80% identity to SEQ ID NO:2 to modify development in a plant.

The specification, on pg 18-19, suggests making conservative substitutions to produce variant proteins. However, making "conservative" substitutions does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1).

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids encoding proteins with 80% identity to SEQ ID NO:2. Making all possible single amino acid substitutions in an 1729 amino acid long protein like that encoded by SEQ ID NO:1 or 5 would require making and analyzing $19^{1729}$ nucleic acids; these proteins would have 99.9% identity to SEQ ID NO:2. Because nucleic acids encoding proteins with 80% identity to SEQ ID

NO:2 would encode proteins with 345 amino acid substitutions, many more than $19^{1729}$ nucleic acids would need to be made and analyzed.

The specification states that SEQ ID NO:2 is related to endonuclease III, based on homology to a protein from *Deinococcus radiodurans* (pg 14, lines 18-20, and pg 40, lines 22-29, and pg 42, lines 4-24). However, this homology spans 191 of SEQ ID NO:2's 1729 amino acids and is only 31.4% similar. The *D. radiodurans* protein was identified in a genomic sequencing project as an endonuclease III by its having 53.3% identity to a protein from *Methanobacterium thermautotrophium* that was identified in a genomic sequencing project as an endonuclease III by its having 35% identity to a putative endonuclease III identified in a *Methanococcus jannaschii* genomic sequencing project (see GenBank Accession Nos. AE002073, AE000855 and Q58030). This was not followed back further, but the point is clear. Identification of the protein of SEQ ID NO:2 as an endonuclease III or a related protein solely by homology to a series of putative endonuclease III proteins, and without other supporting data, like enzymatic activity studies, is speculative at best. Duggleby (1997, Gene 190:245-249) teach that "the function of any DNA sequence, whose identity is based solely on homology, can only be proven by experiments designed to evaluate that function" (pg 248, left column, paragraph 4). Additionally, an endonuclease III gene from *Arabidopsis* has been cloned (Roldán-Arjona et al, 2000, Plant Mol. Biol. 44:43-52). That protein has a very different sequence and is much shorter than the protein of SEQ ID NO:2.

The specification speculates, based on putative presence of a protein motif, that the protein encoded by the instant nucleic acid is an endonuclease III or a glycosylase (pg 42, lines 4-24), particularly a 5 -methylcytosine glycosylase (pg 44, lines 1-24). This conclusion is partly

drawn because a mutation in an unrelated gene results in a reduction in genomic cytosine methylation and also results in phenotypic abnormalities in floral phenotype (pg 12-23). The specification also found weak homology between SEQ ID NO:2 and a series of protein fragments in the sequence databases and used those sequences to derive three consensus sequences, DMT Domains A, B and C (pg 42, line 24, to pg 43, line 28). However, the instant specification provides no evidence that SEQ ID NO:2 or any of these other proteins have the putative enzymatic function. Thus, it is not clear that DMT affects DNA methylation.

The specification teaches no assay to determine if any of the proteins encoded by nucleic acids encoding proteins with 80% identity to SEQ ID NO:2 have "DMT" activity.

As the specification does not describe the transformation of any plant with any nucleic acid encoding a protein that has 80% identity to SEQ ID NO:2, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with a delaying in flowering time, a modulation of chromosomal DNA methylation, or altered expression of the *MEDEA* gene, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant urges that cancellation of claims 1-2, 6-8, 13, 15-21, 24-26 and 30-33 obviates the rejection.

This is not found persuasive, for the reasons given above. The instant scope of enablement rejection is similar to the scope of enablement rejection detailed in the Office action mailed 26 December 2002.

8. Claims 34-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 22 September 2003, as applied to claims 1-2, 6-8, 13, 15-21, 24-26 and 30-33. Applicant's arguments filed 19 March 2004 have been fully considered but they are not persuasive.

The claims are broadly drawn to a method of using any of a multitude of DNA molecules that encode "DMT" proteins with 80% identity to SEQ ID NO:2. In contrast, the specification only describes a method of using a coding sequence from *Arabidopsis* that comprises SEQ ID NO:1. Applicant does not describe other nucleic acids encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Because the sequences are not described, the method of using the sequences to modulate development in a plant is likewise not described, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the compositions used in the claimed methods, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

Applicant urges that cancellation of claims 1-2, 6-8, 13, 15-21, 24-26 and 30-33 obviates the rejection.

This is not found persuasive, for the reasons given above.

9. Claims 34-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is different from the rejection set forth in the Office action mailed 22 September 2003, as applied to claims 15-21 and 32. Applicant's arguments filed 19 March 2004 have been fully considered but do not apply to these new rejections.

Claim 34 lacks antecedent basis for the limitation "the modulated development" in line 5.

Claims 36-37 lack antecedent basis for the limitation "the polynucleotide sequence" in line1.

Claim 43 is indefinite in its recitation of "wherein the delay in flowering is increased by expressing the polypeptide in the plant". This would imply that the plant already has a delay in flowering, and flowering is delayed further by expressing the polypeptide. The parent claim has no requirement that the plant has a delay in flowering before transformation. Thus, an essential method element is missing.

***Double Patenting***

10. Claims 1-3, 6-8, 13, 15-21, 24-26 and 30-33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10-38 of U.S.

Patent No. 6,476,296. The rejection is modified from the rejection set forth in the Office action mailed 22 September 2003, as applied to claims 1-3, 6-8, 13, 15-21, 24-26 and 30-33, due to Applicant's amendment of the claims. Applicant's arguments filed 19 March 2004 have been fully considered but they are not persuasive.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims drawn to plant expression cassettes comprising nucleic acids encoding proteins with 80% identity to SEQ ID NO:2, cells and plants transformed with those expression cassettes, and methods of using the expression cassettes to modulate transcription, as claimed in the issued patent, are identical to or make obvious a method of modifying development in a plant by transformation with an expression cassette comprising nucleic acids encoding proteins with 80% identity to SEQ ID NO:2, as claimed in the instant application, given that the only method step if the instant method is plant transformation. It is noted that SEQ ID NOs:1, 2 and 5 in '296 are identical to SEQ ID NOs:1, 2 and 5 in the instant application.

Applicant urges that the rejection is moot because claims 1-3, 6-8, 13, 15-21, 24-26 and 30-33 are cancelled (response pg 6).

This is not found persuasive because the method claimed in the issued patent makes obvious the method claimed in the instant application because the latter comprises only the first step of the former method. Thus, the plants, cells and expression cassettes claimed in the issued patent also make obvious the instantly claimed method because making or using those products would also only require that same method step.

***Conclusion***

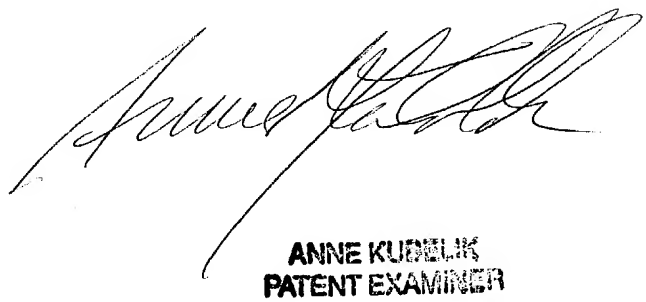
11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (571) 272-0547.

Anne R. Kubelik, Ph.D.
April 15, 2004



ANNE KUBELIK
PATENT EXAMINER